REMARKS

The specification has been amended to correct editorial errors that have heretofore gone unnoticed. No new matter has been added.

Claims 245-317 are pending in the above-referenced application. As will be discussed in further detail below, claims 245, 247, 265, 270, 278, 290, 292, 296, 299, 302, 306, 308 and 309 have been amended to more distinctly claim that which Applicants regard as their invention. The claim amendments are supported by the specification. No new matter has been added. Furthermore, claim 246 has been amended to correct the spelling of "eukaryotic"; claims 247, 278, 301 and 302 have been amended to remove the second recitation of "a phage"; claim 307 have been amended to remove the second "or". Claims 246, 261, 266-267, 269, 275-277, 281, 285, 291, 293-295 and 314-316 have been cancelled.

Furthermore, claims 318-320 have been added to recite a method for introducing the construct of claim 245 into a cell and claims 321-323 have been amended to recite a method for introducing the nucleic acid component of claim 299 into a cell. The claims are supported by the specification.

Applicants will submit formal drawings in a Supplemental Response.

1.The Rejection Under 35 U.S.C. 112, First Paragraph-Written Description

Claims 245-280, 282-284, and 286-317 have been rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention. The Office Action specifically states on pages 13-15:

> The claims lack written description since a representative number of species of the constructs claimed for use in a cell are not adequately

> described by the specification as filed. The claims are drawn to the following independently claimed compositions: ..... As summarized above, one of skill in the art must be able to "immediately envisage the product claimed from the disclosed process..." Although, the specification as filed has shown (in the figures especially) numerous vector-like constructs, the only species shown to produce a product in a cell is that of the intron containing vector constructs for expression of an antisense to HIV expressed therefrom in a cell in cell culture. One of skill in the art would not have recognized that applicant was in possession of a representative number of other species of the broad genus of constructs claimed having other nucleic acid elements which are produced upon expression in a cell. In regards to the breath of antisense claimed, design of an antisense is based on knowledge of the target gene nucleic acid structure. One of ordinary skill in the art would not have recognized that applicant was in possession of a representative number of species of antisense (or ribozyme) to any target gene from the teachings of the specification as filed. .....Furthermore, neither the specification nor the prior art taught a representative number of species of the claimed constructs having the function of use in cells in a whole organism, via, administration either *iv vivo* or *ex vivo*. The examples in the instant specification as filed do not teach the direct correlation between any such vector constructs (including the U1-anti-HIV-constructs) as having a specific function in a cell in a whole organism.

It is further stated in the Office Action on pages 15 and 16:

> In the instant case, the constructs are nucleic acid constructs which when present in a cell produce a product as well as other possible products. This genus claimed embraces the production of a product in any cell. Not all cells are alike, and the environmental conditions alter drastically from use of cells in cell culture to use of cells in a whole

> organism which are intimately connected to other cells in a whole organism. Thus, the genus of cells in which the nucleic acid constructs are expressed is critical to understanding the genus of the claimed constructs since the claims have the function limitation that the nucleic acid construct is introduced into a cell and codes for and expresses a non-native nucleic acid. Additionally, to understand the breath of the claimed genus, one of skill in the art must consider the breath of the nucleic acid constructs claimed. Typically in the art, only a vector-type construct is capable of having the function of coding for and expressing a nucleic acid product from the encoding nucleic acid gene sequence. Since nucleic acid constructs are composed of nucleic acids, having a defined sequence of bases, one of skill in the art would not readily envisage any such nucleic acid construct absent the nucleic acid sequence of said construct. Thus, the claimed genus is extremely broad since it is drawn to any possible nucleic acid construct expressing in a cell. And since the specification as filed does not further provide the essential material of defining the common elements of nucleic acid sequence structure of any such nucleic acid composition, one of skill in the art does not have a clear vision of a representative number of species of any such nucleic acid construct. The invention should be clearly defined in the specification as filed and essential material to the claimed invention (such as the nucleic acid sequences of the claimed nucleic acid constructs) can only be incorporated by reference to a patent publication (see MPEP 608.01 (p) (A)). Thus, the claims are not adequately described by the specification as filed for the breath of claimed constructs.

Applicants respectfully traverse the rejection. Applicants first note that claim 245 has been amended to recite that the primary nucleic acid component when introduced into a cell produces a secondary nucleic acid component

which **produces** a nucleic acid product; claim 265 has been amended to recite that the nucleic acid component in the claimed composition, which when present in a cell produces a non-natural nucleic acid product, which product comprises (i) a nuclear localization sequence comprising a portion of snRNA, said snRNA comprising sequences for at least two stem loops present at the 3' end of native snRNA, and a reimportation signal and (ii) a nucleic acid sequence of interest and claim 299 as amended recites that the nucleic acid component **produces** more than one specific nucleic acid sequence when introduced into a **eukaryotic** cell, each such specific sequence so produced being substantially nonhomologous with each other and being either complementary with a specific portion of one or more single-stranded nucleic acid of interest in a cell or **binds** to a specific protein of interest in a cell. Claims 314-316 have been cancelled.

It is Applicants position that the subject matter recited in the currently pending claims are adequately described in the specification. With respect to the subject matter recited in claims 245, 247-260, 262-264, a definition of "primary nucleic acid construct", "a production center", "propagation", "production" and "inherent cell systems" are provided on pages 91-92. A detailed description of the primary nucleic acid constructs are described on pages 92-100. Specifically, "the propagation of production centers from primary nucleic acid constructs, the propagation of production centers from other production centers and the production of single stranded nucleic acid from production centers" are described in the specification starting with the paragraph bridging pages 97 and 98 and continuing through page 100. As will be discussed in further detail below, various primary nucleic acid constructs are also described in Examples 21-25 and depicted in Figures 34-41.

The nucleic acid component and methods of use, recited in amended claims 265-290 and claims 299-313 are also described in more than adequate

detail in the specification. Specifically, pages 101-104 describe the composition recited in claim 265 and pages 104-110 describe the composition recited in claim 299. Specific examples are provided in Examples 26 and 27 and depicted in Figures 41-47.

Applicants further assert that a representative number of species have been disclosed. Several examples of the primary nucleic acid constructs recited in claim 245 are provided. Specifically, in the specification, four elements for propagation and production are recited:

1) single or multiple promoters,
2) self-priming processes,
3) one or more primer binding sites and
4) multiple priming (pages 98-100).

Furthermore, the following examples are also disclosed:

1) Example 21: A Primary Nucleic Acid Construct that Propagates Production Centers for the Production of Singles-Stranded Antisense
2) Example 22: A Primary Nucleic Acid Construct that Propagates an RNA Production Center that is Reverse Transcribed to Create DNA Production Centers Capable of Directing Transcription
3) Example 23: A Primary Nucleic Acid Construct which Propagates a Double Hairpin Production Center for the Production of Single Stranded RNA
4) Example 24: A Nucleic Acid Construct which Propagates a Production Center capable of Inducible Cell Destruction
5) Example 25: Use of tRNA Primers to Create a Double-Stranded DNA Production Center for Production of Single Stranded RNA

As noted above, specific species of the nucleic acid components recited in claims 265, 268-274, 278-280, 282-284, 286-290, 292 and 296-298 are

disclosed in the specification and Examples 26 and 27 (single and multicassettes).

Applicants take issue with the assertion made in the Office Action that it is necessary to provide the chemical structure of the claimed nucleic acid constructs or components. This assertion is *contra* to the policies stated in the MPEP II.A.3.:

> Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. For example, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, a comparison of enzymatic activities, or antibody cross-reactivity may be sufficient to show possession of the claimed invention to one of skill in the art.

To support Applicants' position, Applicants submit herewith as Exhibit A the following basic texts available at the time of the instant invention.

1. Davis et al., Basic Methods in Molecular Biology, Elsevier, New York, 1986;
2. Old et al., Principles of Gene Manipulation, Blackwell Scientific Publications, London, 1986;
3. Perbal, A Practical Guide to Molecular Cloning, John Wiley & Sons, New York, 1984;
4. Maniatis et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, 1982

Each of these references contain schematic diagrams for obtaining constructs and how they would function. The level of detail used in these references is very similar to that provided in the figures in the instant application. None of

these references placed any restrictions with respect to sequences of the constructs or types of cells that the constructs could be introduced into.

Furthermore, some genetic elements are known to be universal in nature. For instance, all eukaryotic cells express snRNA and carry out the various steps involved in splicing processes. In addition, since gene therapy has been of interest for the past two decades, one of ordinary skill in the art knows which promoters would function best in which cells.

Clearly, the particular sequences of the constructs and nucleic acid components and the types of eukaryotic cells used in the present invention are non-critical features of the invention and thus require no written support. A description need not be provided for features that are not essential or critical to the invention. *Ethicon Endo-Surgery, Inc. v. United States Surgical Corporation, 93 F. 3*d 1572 (Fed. Cir. 1996). An inventor need not explain every detail since he is speaking to those skilled in the art. What is conventional knowledge will be read into the disclosure. *In re Howarth*, 654 F.2d 103, 210 USPQ 689 (CCPA 1981).

Applicants also note that *contra* to the assertions made in the Office Action, the specification actually does disclose that the compositions of the present invention may be administered either *in vivo* or *ex vivo*. The specification on page 13, lines 17-18 cites Yu et al., 1994, Gene Therapy 1:13-26 which is incorporated by reference. Yu et al. actually discloses various methods for administering vectors into cells in culture as well as into whole organisms. A copy of Yu et al. is attached hereto as Exhibit B. Furthermore, methods for *in vivo* and *ex vivo* administration were well known in the art for expressing a nucleic acid product in a whole organism. Examples of such teachings are attached hereto as Exhibit C:

1. Miller and Vile, 1995, "Targeted vectors for gene therapy", FASEB J 9:190-199;

2. Ally et al., 1995, "Prevention of autoimmune disease by retroviral mediated gene therapy", J. Immunol. 155:5404-5408;

3. Lau et al., 1995, "Retroviral gene transfer into the intestinal epithelium", Hum. Gene Ther. 6:1145-1151

In view of the above arguments and amendments to claims 245, 265 and 299, Applicants assert that the rejections over 35 U.S.C. 112, first paragraph (written description) have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

2. The Rejections Under 35 U.S.C. 112, First Paragraph-Lack of Enablement

Claims 260-263 and 284–298 are rejected under U.S.C. 112, first paragraph, lack of enablement. In the Examiner's view, the specification, while being enabling for methods of selectively expressing a nucleic acid product in a cell in cell culture (*in vitro*), does not reasonably provide enablement for methods of expressing the nucleic acids in a whole organism (*in vivo*).

The Office Action specifically states on page 19:

> The specification teaches several constructs designed for entry into a cell and expression of one or more sequences to perform a biological function such as antisense inhibition of a nucleic acid. Specifically, several CHENAC constructs are taught prophetically, and pictured in figures 1-13 as vector based constructs constructed by using modified nucleic acid regions and designed to provide improved entry into a cell by way of improved construct-cell interaction. A second group of nucleic acid fused with antibody based constructs are taught prophetically and shown in figures 14-21. Preparation of multimeric insulin by means of nucleic acid hybridization is further taught prophetically and shown in figures 22-23. No exemplification for such constructs is taught in the specification as filed.

The Examiner focused on expression of antisense and ribozymes in this rejection because in her view,

> Since the only constructs reduced to practice in the specification as filed are the U1-vector-antisense constructs, the instant rejection will focus on the use of these constructs in cells in a whole organism versus cells in cell culture

With respect to antisense and ribozymes, the Examiner on pages 22-23 states:

> There is a high level of unpredictability known in the antisense and relative ribozyme art for *in vivo* (whole organism) applications. The following references primarily refer to the unpredictability of administration of antisense oligonucleotides, but may also be applied to antisense expressed from a vector since the function of the antisense is the same, to locate and bind a target gene, thereby decreasing its expression.

It is concluded in the paragraph bridging pages 24-25:

> One of skill in the art would not accept in its face the successful delivery of the disclosed antisense molecule constructs *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo* (2) effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatments effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed.

> Therefore, it would require undue experimentation to practice the invention as claimed.

The Examiner further states:

> The above rejection does not imply that an animal model of a disease is needed to enable the instantly claimed invention. The rejection is centered on the ability to make and use the claimed methods with any expression construct as claimed, and the position has been maintained, based on the references cited, that there is a high level of unpredictability in the art of design and use of antisense in a whole organism. Although applicants state that clinical trials are underway, the information in Exhibit 4 does not teach what constructs are in the trials and whether or not they function as instantly claimed in the context of a whole organism.

Applicants respectfully traverse the rejection. First, Applicants assert that methods were well known in the art for obtaining stable antisense and ribozyme molecule constructs and methods for their delivery into cells at the time of the priority date of the instant application. Examples are provided in Exhibit C:

1. Wang et al., 1995, "Delivery of antisense oligodeoxyribonucleotides against the human epidermal growth factor receptor into cultured KB cells with liposomes conjugated to folate via polyethylene glycol", Proc. Natl. Acad. Sci. USA 92:3318-3322;
2. Vlassov et al., 1993, "Penetration of oligonucleotides into mouse organism through mucosa and skin", FEBS Lett. 327:271-274;
3. Agarwal et al., 1995, "Absorption, Tissue Distribution and In Vivo Stability in Rates of a Hybrid Antisense Oligonucleotide Following Oral Administration", Biochem. Pharmacol. 50:571-576;

4. Rossi, 1995, "Controlled, targeted, intracellular expression of ribozymes: progress and problems", Trends Biotechnol. 13:301-306.

Furthermore, the antisense sequences which are described to be inserted into a construct containing U1 sequences (see Example 26) are also used in Example 19, Antisense to (A), Antisense to (B) and Antisense to (C). As noted in the specification, Antisense to (A) was derived from Joshi et al. (1991 J. Virol. 65, 5524) and Antisense to (B) was derived from Sczakiel et al. (1990 Biochem. Biophys. Res. Comm. 169, 213). These two references actually disclosed the effective inhibition of HIV-1 replication by antisense action.

Applicants note that the law does not require a specification to be a blueprint in order to satisfy the requirement for enablement under 35 USC 112, first paragraph. Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be. *Staehlin v. Secher* 24 USPQ2d 1513, 1516 (BPAI 1992). The law does not require an applicant to describe in his specification every conceivable embodiment of the invention. *U.S. v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

Furthermore, it is Applicants position that it would not require undue experimentation to go from the *in vitro* studies to *in vivo* studies. First, *contra* to assertions made in the Office Action, it is not so unpredictable that a nucleic acid component when present in a cell produces a nucleic acid product comprising a nucleic acid sequence of interest and a localization signal, a secondary component that produces a nucleic acid product or tertiary component, or a plurality of nucleic acid sequences that may be an antisense, sense or protein binding nucleic acid sequence or ribozyme would be effective *in vivo*.

The Office Action cites a number of references purporting to illustrate the unpredictability of antisense technology. However, as noted in the Office Action, the references cited all concern the use of antisense oligonucleotides **not** constructs containing antisense sequences. Therapeutics based on oligonucleotides offers a pharmaceutical approach whereas the use of the plasmids to generate antisense RNA inside the cell involve a gene therapy approach. The method of the present invention uses a construct that produces an antisense. Applicants submit as Exhibit D, the following references showing the correlation between in vivo and in vitro results using both oligonucleotides, ribozyme, RNAi sequences and vectors containing antisense sequences:

1. Opalinska and Gewirtz, 2002, "Nucleic-acid Therapeutics: Basic Principles and Recent Applications", Nature Reviews, Drug Discovery 1:503-514 (hereinafter Opalinska and Gewirtz, 2002). Applicants note that one of the references cited by the Examiner as evidence of predictability, Jen, was coauthored by Gewirtz. However, Opalinska and Gewirtz, 2002, disclose that a number of clinical trials in Phase II/III are currently underway with antisense compounds and express optimism that these compounds will prove to be efficacious;
2. Stone et al., 2003, "The pain of antisense: in vivo application of antisense oligonucleotides for functional genomics in pain and analgesia", Adv. Drug Del. Rev. 55:1081-1112 (Stone et al., 2003). Specifically, Stone et al. states on page 1089, column 1, lines 31-38:

> The potential for discrepancies between in vivo and in vitro efficacies does not discount the possible benefits of selecting active ASOs in an in vitro system provided such a system is easily available, is optimized and models closely the cell types to be

targeted in vivo (for example, using neuroblastoma cell lines for CNS targets)

3. Wang et al., 1999, "Antitumor activity and pharmacokinetics of a mixed-backbone antisense oligonucleotide targeted to the R1A subunit of protein kinase A after oral administration", Proc. Natl. Acad. Sci. USA 96:13989-13994, discloses a correlation between in vitro and in vivo results;
4. Voorhoeve and Agami, 2003, "Knockdown Stands Up", Trends in Biotechnology 21:2-4, reviews the correlation of in vitro and in vivo results using RNAi;
5. Vacek et al., 2003, "Antisense-mediated redirection of mRNA splicing", Cell. Mol. Life Sci. 60:825-833, discuss how therapeutics based on oligonucleotides offers a pharmaceutical approach whereas the use of the plasmids to generate antisense RNA inside the cell involve a gene therapy approach and also summarize studies conducted with both oligonucleotides and plasmids;
6. Kelley et al., 2003, "CaSm antisense gene therapy: a novel approach for the treatment of pancreatic cancer", Anticancer Res. 23:2007-13 discloses that an adenovirus expressing antisense RNA to the CaSm gene is able to reduce endogenous CaSm mRNA expression in vitro and extends survival in an in vivo SCID mouse model of human pancreatic cancer;
7. Xu et al., 2003, "Molecular Therapeutics of HBV", Current Gene Therapy 3: 341-355 discloses the use of antisense RNA and DNA as oligonucleotides and expressed in vectors and hammerhead ribozymes for treating HBV infection.

Applicants note that it is stated in the MPEP §2107.03 that "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process". Given that a correlation can be established between the *in vitro* assays and the asserted utility, *in vivo* studies are not necessary. Furthermore, it would not constitute undue experimentation to design and use , e.g., antisense in the whole organism.

In view of the above arguments, Applicants assert that the rejections under 35 U.S.C. 112, first paragraph, lack of enablement have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

3. The Rejections Under 35 U.S.C. 102(e)

3.1 Sullenger et al.

Claims 265-270, 272-276, 278-280, 282-284 and 288-295 have been rejected under 35 U.S.C. 102(e) as being anticipated by Sullenger et al. (U.S. Patent 5,854,038). With respect to Sullenger, the Office Action states on pages 29-32:

> ...Sullenger et al. taught in column 3, lines 8-37, specifically lines 15-20, that "[t]hese localisation signals may be tethered to the therapeutic agent by any desired procedure, for example, by construction of a DNA template which produces both the localization signal and therapeutic agent RNA as part of the same RNA molecule. They taught in col. 2, lines 38-48, that the therapeutic agents that are localized in an appropriate compartment with a viral target include RNA molecules such as decoy RNAs, ribozymes and antisense RNA or DNA molecules.....

> ....In col. 10 of Sullenger et al., lines 57-58, they further teach use of "localization to nuclear compartment utilizing antigen binding site found on most snRNAs". See also col. 3, lines 5-7, which teach localization to "a nucleus at the location of synthesis of the target."
>
> .....In col. 6 lines 7-31, Sullenger et al. taught that plasmid vectors may be used to expressed the localized nucleic acid constructs.
>
> ....Sullenger et al. taught throughout the specification that their constructs are for use in targeting cells, and specifically, locations within cells, or specific tissues, with their disclosed therapeutic nucleic acid targeted constructs.

Applicants respectfully traverse the rejection. Applicants note that in order to advance prosecution, claim 265 has been amended to recite that the composition of the present invention comprises a nucleic acid component, which when present in a cell produces a non-natural nucleic acid product, which product comprises two elements: (i) **a nuclear localization sequence comprising a portion of snRNA, said snRNA comprising sequences for at least two stem loops present at the 3' end of native snRNA, and a reimportation signal** and (ii) a nucleic acid sequence of interest. The other claims rejected, 266-270, 272-276, 278-280, 282-284 and 288-295 either directly or indirectly depend from claim 265. Applicants note that claims 266-267, 269, 275-277, 281, 285, 291 and 293-295 have been cancelled.

It is well established case law that anticipation can only be established by a single prior art reference which discloses each and every element of the claimed invention; anticipation is not shown even if the differences between the claims and the prior art reference are argued to be "insubstantial" and the missing elements could be supplied by the knowledge of one skilled in the art. *Structural Rubber Prod. Co. v. Park Rubber Co.*, 221 U.S.P.Q. 1264 (Fed. Cir. 1984). Furthermore, in *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225

U.S.P.Q. 253 (Fed. Cir. 1985) the court pointed out that the assertion of invalidity for lack of novelty if the prior art disclosed "substantially the same thing" is erroneous. The prior art reference in question must meet each claim limitation in order to constitute anticipation.

In Applicants view, the remaining pending rejected claims are not anticipated by Sullenger et al. All of the elements of amended claim 265 are certainly not recited in Sullenger et al. Specifically, there is no disclosure in Sullenger et al. regarding the nuclear localization signal containing a portion of an snRNA containing at least two loops and a reimportation signal. All that is stated is that with respect to snRNAs is in the context of delivery of an agent in column 10, lines 57-58:

> "d. localization to nuclear compartment utilizing antigen binding site found on most snRNAs"

In view of the amendments to the claims and the above arguments, claims 265-270, 272-276, 278-280, 282-284 and 288-295 are not anticipated by Sullenger et al. Applicants therefore respectfully request that the rejections be withdrawn.

3.2 DeYoung et al.

Claims 245-249, 251-256, 258-261, 264-273, 275, 278-279, 282-283, 284, 288, 289, 290-296, 299, 300, 302, 303, 308, 312, and 313 are rejected under 35 U.S.C. 102 (b) as being anticipated by DeYoung et al. (*Biochemistry* Vol. 33 pp. 12127-12138, 1994). With respect to claims 245 and 246, the Office Action states on page 33:

> Claims 245 and 246 are drawn to a composition comprising a primary nucleic acid component which upon introduction into a eukaryotic cell produces a secondary nucleic acid component which is capable of producing a nucleic acid product, or a tertiary nucleic acid component, or both, in said eukaryotic cell, wherein said primary nucleic acid component is

> not obtained with said secondary or tertiary component or said nucleic acid product. Since the composition comprising the primary nucleic acid component which upon introduction into a eukaryotic cell produces a secondary nucleic acid component which is merely 'capable of' producing a nucleic acid product, or a tertiary nucleic acid component or both, the language 'capable of' implies a latent characteristic of the claimed nucleic acid composition, but does not require this property.
>
> De Young et al. taught on page 12128, col. 1 that "[w]e report here the use of U1 and T7 vector systems to direct the expression of ribozyme constructs of limited and defined size that are sufficiently stable to efficiently cleave ANF mRNA in cells. These vector systems ...should be applicable to the selective suppression of other desired genes, either for physiological studies or for therapeutic purposes." In figure 3, page 12129, they taught the vector constructs used for expression of the U1-ribozyme constructs. Thus they taught the instantly claimed primary and secondary nucleic acid component claimed (the primary is the vector, the secondary is the expressed U1-ribozyme in the cell).

In response and in order to advance prosecution, claim 245 has been amended to recite that the primary construct when introduced into a cell produces a secondary nucleic acid component which **produces** a nucleic acid product, or a tertiary nucleic acid component, or both. The U1-ribozyme construct of DeYoung does not actually produce a nucleic acid product or tertiary nucleic acid product. Claims 246-249, 251-256, 258-261and 264 depend either directly or indirectly from claim 245. Claims 246 and 261 have been cancelled.

The Office Action states in the paragraph bridging pages 35-36 with respect to claims 265-267 and 269-271:

> DeYoung et al. further anticipated claims 265 – 267 and 269-271 since they taught a composition of matter comprising a nucleic acid component (the vectors in figure 3) which when present in a cell produces a non-natural product (the U1-ribozyme constructs), which product comprises (I) a cellular compartment localizing entity (the U1 snRNA sequence which localizes to the nucleus), and (ii) a nucleic acid ribozyme expressed is an RNA sequence.

Applicants, in response, note that in order to advance prosecution and more distinctly claim the subject matter which Applicants regard as their invention, claim 265 has been amended. Specifically, as noted above, claim 265 now recites the composition of the present invention comprises a nucleic acid component, which when present in a cell produces a non-natural nucleic acid product, which product comprises two elements: (i) **a nuclear localization sequence comprising a portion of snRNA, said snRNA comprising sequences for at least two stem loops present at the 3' end of native snRNA, and a reimportation signal** and (ii) a nucleic acid sequence of interest. In contrast, the construct shown in DeYoung et al. only contained initiation and termination sequences of U1. Specifically, it is stated in DeYoung et al. on p.12129, lines 20-28:

> Since *in vitro* transcription of the RNA polymerase II-activated U1 promoter is problematic (citation omitter), a PCR approach was used to produce chimeric DNA, which encoded the T7 promoter, the U1 initiation sequence and the ribozyme and U1 termination sequences, from pU1RZ. This PCR product was then used as a template to allow T7 RNA polymerase-mediate *in vitro* transcription, to express ribozymes with U1 initiation and termination sequences.

Furthermore, predicted structures of U2-B, U1-H and U1-I_{U7C} are shown in Figure 8. However, none of these structures actually contained all of the elements of the recited snRNA sequence.

Additionally, claims 266-267 and 269 has been cancelled. Claims 270-271 depend directly or indirectly from claim 265.

With respect to claim 299, the Office Action states in the paragraph bridging pages 36-37:

> Claim 299 is anticipated by DeYoung et al. since their plasmid U1snRNA constructs are nucleic acid components which upon introduction into a cell express the ribozyme constructs. Since the language use is claim 299, 'capable of', is a latent characteristic as claimed, the claim broadly embraces any nucleic acid component such as those taught by DeYoung et al. Furthermore, De Young et al. anticipates instant claim 300 since the single-stranded nucleic acids of interest are the ribozymes taught by DeYoung et al.

In response and as noted above, claim 299 has been amended to recite that the nucleic acid component which upon introduction into a eukaryotic cell **produces** more than one specific nucleic acid sequence, each such specific sequence so produced being substantially nonhomologous with each other and being either complementary with a specific portion of one or more single-stranded nucleic acid of interest in a cell or **binds** to a specific protein of interest in a cell. Clearly, amended claim 299 is not anticipated by DeYoung et al. Claims 300, 302, 303, 308, 312, and 313 depend directly or indirectly from claim 299. Applicants note that claim 302 has been cancelled.

In view of amended claims 245, 265 and 299 and the above arguments, Applicants assert that the rejections over DeYoung et al. have been overcome. Therefore, Applicants respectfully request that the rejections over DeYoung et al. under 35 U.S.C. 102(b) be withdrawn.

3.3 Hinuma et al.

Claims 245, 249, 250, 265, 276, 277, 279, 280 and 314-316 have been rejected under 35 U.S.C. 102 (e) as being anticipated by Hinuma et al. (U.S. Patent 6,538,107). The Office Action specifically states on pages 38-39:

> Hinuma et al teaches in col. 105-106 that antisense oligonucleotides (nucleic acids) capable of inhibiting the replication or expression of G protein coupled receptor protein gene. They state that the "relationship between the target and oligonucleotides complementary to at least a portion of the target, specifically hybridizable with the target, is denoted as "antisense"." (col. 105, lines 31-34) They state that the antisense "may include double – and single-stranded DNA, as well as double –and single-stranded RNA and DNA:RNA hybrids, and also include, as well as unmodified forms of the polynucleotide or oligonucleotide, known types of modifications, for example, labels which are known to those skilled in the art, "caps", methylation, substitution of one or more of the naturally occurring nucleotides with analogue, internucleotide modifications such as, for example, those with uncharged linkages (e.g. methyl phosphonates, phosphotriesters, phosphoramidates, cabamates, etc.) and with charged linkages or sulfur-containing linkages (e.g. phosphorothioates, phophorodithioates, etc.), those containing pendant moietes, such as, for example proteins (including nucleases, nuclease inhibitors, toxins, antibodies, signal peptide, poly-L-lysine, etc.) and saccharides (e.g. monosaccharides, etc.) those with intercalators (e.g. acridine, psoralen, etc.) those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g. alpha anomeric nucleic acids, etc.) (Col. 105, lines 44-64) See also the rest of col. 105 and col. 106 for additional information taught by Hinuma et al. for the modification of such antisense.

> Thus, Hinuma et al. taught all the elements of the instantly claimed invention since they taught double-stranded (complementary, hybridized) oligonucleotides which are tails since they are linear and have an end. These oligonucleotides may be modified with covalently bound moieties such as antibodies or signal peptides and also when in a cell are capable of producing a product by the antisense action of the molecules which decreases expression of the target gene (thus the product is the decreased gene expression) and/or other actions of the attached molecules. Since they taught conjugation with signal peptides, they taught use of these conjugates for direction to a particular cellular compartment.

Applicants respectfully traverse the rejection. As has been previously noted, claim 245 has been amended to recite that the primary nucleic acid component which upon introduction into a eukaryotic cell produces a secondary nucleic acid component which produces a nucleic acid product, or a tertiary nucleic acid component, or both, in said eukaryotic cell. There is no such teaching in Hinuma et al. In Hinuma et al., there is merely the teaching of the use of antisense, not transcription of a construct encoding antisense (primary nucleic acid component) to obtain a secondary nucleic acid component , the transcript and subsequent reverse transcription to a single-stranded anti-sense sequence, the nucleic acid product produced (see Figure 34). Claims 249 and 250 depend from claim 245 and thus is not anticipated by claim 245.

As also previously noted, claim 265 has additionally been amended to recite that the composition of the present invention comprises a nucleic acid component, which when present in a cell, produces a non-natural nucleic acid product, which product comprises two elements: (i) **a nuclear localization sequence comprising a portion of snRNA, said snRNA comprising sequ nces for at l ast two stem loops pres nt at the 3' end of native snRNA,**

and a reimportation signal and (ii) a nucleic acid sequence of interest. There is absolutely no teaching of the nuclear localization sequence recited in claim 265 in Hinuma et al. Claims 276, 277, 279 and 280 depend directly or indirectly from claim 265. Applicants further note that claims 276-277 have been cancelled. Therefore, these claims would also not be anticipated by Hinuma et al.

Finally, claims 314-316 have been cancelled.

Given the amendment of claims 245 and 265 and the cancellation of claims 276-277 and 314-316, Applicants assert that the rejections over Hinuma et al. have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

4. The Obviousness Rejections

Claims 245, 256, 257, 265, 317, 273 and 274 have been rejected under 35 U.S. C. 103 (a) as being unpatentable over Sullenger et al. (U.S. Patent 5,845,038) or De Young et al. (*Biochemistry* Vol. 33,pp.12127-12138, 1994) in view of ter Meulen et al. (U.S. Patent 5,646,032). The Office Action specifically states on pages 41-42:

> Sullenger et al. taught in column 3, lines 8-37, specifically lines 15-20, that "[t]hese localization signals may be tethered to the therapeutic agent by any desired procedure, for example, by construction of a DNA template which produces both the localization signal and therapeutic agent RNA as part of the same RNA molecule. They taught in col. 2, lines 38-48, that the therapeutic agents that are localized in an appropriate compartment with a viral target include RNA molecules such as decoy RNAs, ribozymes and antisense RNA or DNA molecules.
>
> They did not teach that the target was a viral replication gene/agent.

ter Muelen et al. taught in col. 4, lines 17-25, that "decoy RNA may be used that contains particular nucleotides base sequences which, for their part, bind virus proteins which are essential for the replication of a pathogenic virus. Thus, decoy RNA sequences can, for example, contain multiple copies of the TAR nucleotide base sequence and the REV responsive element nucleotide base sequence (RRE) from HIV and competitively bind the tat and rev regulatory proteins of HIV, and thereby lower the rate of replication of HIV in the infected cell."

It would have been *prima facie* obvious to one of ordinary skill in the art to substitute the antisense or decoy RNA and/or DNA molecule taught by Sullenger et al. with the decoy taught by ter Muelen et al. directed against a viral replication target since Sullenger taught the design of decoys generally to any viral target, and as ter Muelen et al. taught, the viral replication target since Sullenger taught the design of decoys generally to any viral target, and as ter Muelen et al taught, the viral replication protein is an essential molecule for the replication of the virus and targeting this sequence with a decoy allows for competitive binding to lower the rate of viral replication in the infected cell.

One of ordinary skill in the art would have been motivated to inhibit an infectious virus as taught both by Sullenger et al and ter Muelen et al. with agents such as decoys to inhibit virus. Although Sullenger et al. does not explicitly recite targeting viral replication *per se*, ter Muelen et al. taught that one of ordinary skill is the art would have been motivated to target viral replication using decoys for the benefits of lowering the rate of replication of the virus in the infected cell.

One of ordinary skill in the art would have had an expectation of success to use decoy constructs taught by Sullenger et al to produce a decoy in a virally infected cell such as taught by ter Muelen et al for the purpose of lowering the rate of the replication of the virus in the infected cell.

Applicants respectfully traverse the rejection. Although nothing was said with respect to DeYoung et al. in the obviousness rejection, Applicants will address that reference as well. As noted above, the composition of claims 245, 256, 257, 265, 317, 273 and 274 can be distinguished from both Sullenger and DeYoung. With respect to the compositions of claims 245, 256, 257, and 317, neither Sullenger nor DeYoung disclosed or suggested a composition comprising a primary nucleic acid component which upon introduction into a eukaryotic cell produces a secondary nucleic acid component which produces a nucleic acid product, or a tertiary nucleic acid component, or both, in said eukaryotic cell. In the constructs of Sullenger and DeYoung there is merely production of a nucleic acid product from the construct in a cell. There is no teaching or suggestion of a primary nucleic acid construct which when introduced into a cell produces **a secondary nucleic acid component** which ultimately produces a nucleic acid product.

With respect to claims 265, 273 and 274, as noted above, there is no suggestion or disclosure in either Sullenger or DeYoung regarding a composition producing in addition to a sequence of interest, **a nuclear localization sequence comprising a portion of snRNA, said snRNA comprising sequences for at least two stem loops present at the 3' end of native snRNA, and a reimportation signal.** There is no discussion in Sullenger regarding the secondary structure of the localization signal. In DeYoung et al., the focus of the discussion of secondary structure is actually on the effect of U1 sequences on ribozyme function. It is stated in DeYoung et al. on p. 12136, last paragraph:

> In addition to a potential stem and loop structure at the 3' end of U snRNAs, there is a conserved sequence [GTTNo—3AAA(G/A)NNAGA], the 3' end

> box] in the immediate flanking region...The conserved 3' end box is the only element absolutely required for precursor 3' end formation.

Thus, one of ordinary skill in the art would not given the teachings of Sullenger and DeYoung et al. consider the importance of using a nucleic acid component that would produce a portion of an snRNA containing at least two loops and a reimportation signal. It is therefore, Applicants position that the subject matter encompassed by claims 245, 246, 265, 273 and 274 would not be obvious in view of DeYoung or Sullenger.

The secondary reference, ter Meulen, would not add anything of significance. ter Meulen is directed to "foamy virus vectors" and is totally unrelated to the present invention.

The combination of Sullenger or DeYoung with ter Meulen et al. would also not be obvious, since there would be no motivation to combine these references. The system of ter Meulen is totally different from that taught in DeYoung and Sullenger. Specifically, ter Meulen is directed to "foamy virus vectors" and expression of exogenous nucleic acids in these particular vectors. The focus of ter Meulen et al. was certainly not decoys. One of ordinary skill in the art would certainly not look to the teaching of ter Meulen with respect to alternative decoys. If the teachings of two or more references are combined, there must be some logical reason or motivation, apparent from positive concrete evidence of record, which justifies a combination of primary and secondary references. *In re Regel* 526 F.2d 1399 (CCPA 1975). Although the test for establishing implicit teaching, motivation, or suggestion in prior art is what combination of prior art statements would have suggested to those of ordinary skill, such statements must be considered in context of teaching of entire reference, and cannot be viewed in abstract, and rejection of claims cannot be predicated on mere identification in prior art reference of individual

components of claimed limitations; rather, particular findings must be made as to reason skilled artisan, with no knowledge of claimed invention, would have selected these components for combination in manner claimed. *In re Kotzab* 55 USPQ2d 1313 (Fed Cir. 2000).

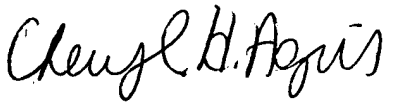
In view of the above arguments, the rejected claims are not obvious over Sullenger et al. or DeYoung et al. in view of ter Meulen et al. Therefore, Applicants respectfully request that the obviousness rejection be withdrawn.

Summary and Conclusions

Claims 245-317 are presented for further examination. Claims 246, 261, 266-267, 269, 275-277, 281, 285, 291, 293-295 and 314-316 have been cancelled. Claims 318-322 have been newly presented.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,



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